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ORIGINAL RESEARCH

Cost-Effectiveness Analysis of Bezlotoxumab Added to Standard of Care Versus Standard of Care Alone for the Prevention of Recurrent *Clostridium difficile* Infection in High-Risk Patients in Spain

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ABSTRACT

Introduction: *Clostridium difficile* infection (CDI) is the major cause of infectious nosocomial diarrhoea and is associated with considerable morbidity, mortality and economic impact. Bezlotoxumab administered in combination with standard of care (SoC) antibiotic therapy prevents recurrent CDI. This study assessed the cost-effectiveness of bezlotoxumab added to SoC, compared to SoC alone, to prevent the recurrence of CDI in high-risk patients from the Spanish National Health System perspective.
Methods: A Markov model was used to simulate the natural history of CDI over a lifetime horizon in five populations of patients at high risk of CDI recurrence according to MODIFY trials: (1) ≥ 65 years old; (2) severe CDI; (3) immunocompromised; (4) ≥ 1 CDI episode in the previous 6 months; and (5) ≥ 65 years old and with ≥ 1 CDI episode in the previous 6 months. The incremental cost-effectiveness ratio (ICER) expressed as cost per quality-adjusted life-year (QALY) gained was calculated. Deterministic (DSA) and probabilistic sensitivity analyses (PSA) were performed.
Results: In all patient populations (from 1 to 5), bezlotoxumab added to SoC reduced CDI recurrence compared to SoC alone by 26.4, 19.5, 21.2, 26.6 and 39.7%, respectively. The

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resulting ICERs for the respective subgroups were €12,724, €17,495, €9545, €7386, and €4378. The model parameters with highest impact on the ICER were recurrence rate (first), mortality, and utility values. The probability that bezlotoxumab was cost-effective at a willingness-to-pay threshold of €21,000/QALY was 85.5%, 54.1%, 86.0%, 94.5%, 99.6%, respectively.

Conclusion: The results suggest that bezlotoxumab added to SoC compared to SoC alone is a cost-effective treatment to prevent the recurrence of CDI in high-risk patients. The influence of changes in model parameters on DSA results was higher in patients ≥ 65 years old, with severe CDI and immunocompromised. Additionally, PSA estimated that the probability of cost-effectiveness exceeded 85% in most subgroups.

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Keywords: Bezlotoxumab; *Clostridium difficile* infection; Cost-effectiveness

INTRODUCTION

Clostridium difficile infection (CDI) is the major cause of infectious nosocomial diarrhoea and is associated with considerable morbidity and mortality, as well as a significant economic impact on the healthcare systems of developed countries [1]. The incidence of CDI increased by 70% in European countries from 4.1 to 7.0 cases per 10,000 patient-bed days between 2008 and 2013, without taking into account the existence of a considerable number of potentially missed CDI diagnoses due to the frequent use of suboptimum laboratory diagnostic tests [2]. In Spain, the estimated figure was 3.2 cases per 10,000 patient-bed days in 2013 [2], with half of the episodes underdiagnosed [3].

The clinical burden of CDI ranges from symptomless carriage, through mild or moderate diarrhoea, to fulminant and sometimes fatal pseudomembranous colitis [4]. One of the main complications in treating CDI is the recurrence of the infection [5] defined as CDI which reoccurs within 8 weeks after the onset of a previous episode, provided the symptoms from the

previous episode resolved after completion of initial treatment [6]. Most patients with an initial CDI episode respond to antibiotic treatment; however, up to 25% of patients may experience CDI recurrence within 30 days following treatment. Patients who experienced a recurrent episode of CDI have a 45% probability of a second recurrence, and this risk increases with each subsequent recurrence [1, 7]. Several risk factors have been identified for the development of recurrent CDI; however, certain subgroups of patients are more susceptible to recurrence such as patients of an older age, immunocompromised individuals those with a history of CDI or patients with an initial clinically severe CDI episode [8–16].

The economic burden of CDI is a result of extended length of hospital stay (LoS), re-admission, laboratory tests and medication. In Spain, the cost for treating *C. difficile*-associated diarrhoea (CDAD) was estimated at €32.2 million to the National Health System (NHS) in 2012 [17]. On average, the cost per episode was €3901, €4875 and €5916, for initial infection, first and second recurrence, respectively. The main extra CDI-associated costs were due to the extended LoS which was 7.4, 9.1 and 10.8 days for initial infection, first and second recurrence, respectively [17].

Bezlotoxumab is a new antitoxin agent (a human monoclonal antibody against *C. difficile* toxin B) which, administered during the course of antibiotic therapy for CDI, is indicated for the prevention of CDI recurrence in adults at high risk of CDI recurrence [18].

The phase III MODIFY I and MODIFY II trials [19] evaluated the efficacy and safety of a single intravenous infusion of bezlotoxumab compared to placebo in patients receiving standard of care (SoC) oral antibiotic therapy for CDI (metronidazole, vancomycin or fidaxomicin). Results from pooled data analysis showed a significantly lower rate of recurrent CDI with bezlotoxumab than placebo in all participants [16.5% (129 of 781) vs. 26.6% (206 of 773); adjusted difference, − 10.0 percentage points; 95% confidence interval (CI), − 14.0 to − 6.0; *p* value < 0.0001]. Moreover, the absolute difference in CDI recurrence rate between bezlotoxumab and placebo was greater in

subpopulations at high risk of CDI recurrence than in the overall population.

Bezlotoxumab has been recently obtained the marketing authorization in Spain [20]. Although many studies have assessed the cost-effectiveness of antibiotic therapy for CDI [21], only one published cost-effectiveness analysis evaluating bezlotoxumab from a US payer perspective has been performed [22]. Due to the increasing burden of CDI and the efficacy of bezlotoxumab in reducing CDI recurrence, our aim was to assess the cost-effectiveness of bezlotoxumab in addition to SoC antibiotic therapy as compared to SoC alone for the prevention of recurrence in five subgroups of patients at high risk of CDI recurrence within the context of the Spanish NHS.

METHODS

Model Overview

A computer-based Markov health state transition model was developed in Microsoft Excel® based on MODIFY I/II trials [19]. The model was previously adapted to the US setting [22] and for the present study the model was adapted to the Spanish context using local data.

The model evaluated the cost-effectiveness of a single dose of bezlotoxumab 10 mg/kg administered as an intravenous infusion compared to placebo for the prevention of recurrence in five patient populations with CDI at increased recurrence risk according to MODIFY I/II trials [19]: (1) aged 65 years or older; (2) clinically severe CDI (defined as a Zar score ≥ 2; scores range from 1 to 8, with higher scores indicating more severe infection); (3) compromised immunity (determination made on the basis of medical history or use of immunosuppressive therapy for hematological malignancy—including leukemia, lymphoma, multiple myeloma—, an active malignancy requiring recent cytotoxic chemotherapy, receipt of a prior hematopoietic stem cell transplant, receipt of a prior solid organ transplant, asplenia, or neutropenia/pancytopenia due to other conditions); (4) a history of CDI (≥ 1 CDI episode in the previous 6 months); (5) aged 65 years or older and a history of CDI (≥ 1 CDI episode in the previous 6 months). The model structure is shown in Fig. 1. A cohort of patients entered the model with mild/moderate or a severe CDI episode. Patients with mild/moderate CDI could experience a clinical cure or a clinical failure. In addition, subjects with severe CDI could undergo colectomy
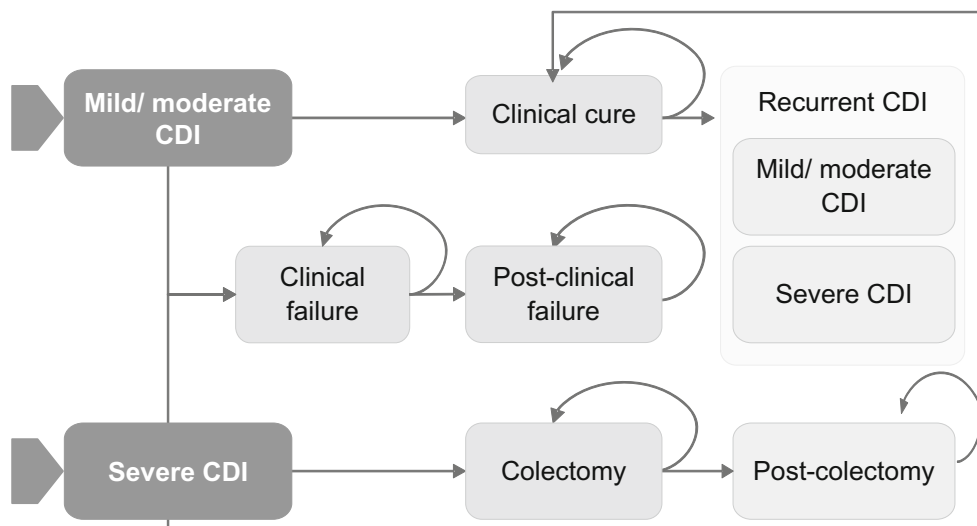
All health states have transitions to death.

Fig. 1 Markov model structure. All health states have transitions to death

surgery. Clinical cure and clinical failure were defined as per the MODIFY I/II trials [19]: (1) clinical cure: subject received ≤ 14-day regimen of SoC therapy and had no diarrhoea (≤ 2 loose stools per 24 h) for 2 consecutive days following completion of SoC therapy for the baseline CDI episode; and (2) clinical failure: subject required > 14-day regimen of SoC therapy for the baseline CDI episode.

Patients experiencing relief from CDI symptoms (clinical cure health state) can experience a mild/moderate or severe recurrence of CDI. Sustained response is achieved by those who remain in the clinical cure health state permanently without experiencing subsequent recurrence or death.

A patient experiencing clinical failure is treated further and eventually cured (post-clinical failure health state). In the current analysis, it was assumed that patients in post-clinical failure health state would not experience any recurrence of CDI since these patients were not followed in MODIFY I/II trials, and the efficacy of bezlotoxumab in addition to SoC was only assessed in those who had a clinical cure. Therefore, it was assumed that the consequences of these patients would not differ between treatment arms.

Patients who have experienced a colectomy move to a post-colectomy health state and are unable to experience a recurrence since CDI symptoms are characterized by colitis.

Death may occur in any health state.

The natural history of CDI is repeated for each recurrence, with a maximum of three possible recurrences.

Cycle Length, Time Horizon and Discount Rates

Given the acute nature of CDI illnesses and that the majority of recurrences occur within 30 days of initial infection, most of the costs are incurred within the first 6 months (180 days) following infection. Therefore, the cycle length was 15 days for the first 180 days, and annual thereafter.

The model assumed a lifetime horizon in order to ascertain the costs and benefits over the patient's lifetime.

A 3% annual discount rate was adopted for both costs and benefits [23].

Model Inputs

Population characteristics (age at model entry, proportion of females, proportion of patients entering the model with severe CDI), first recurrence rate, severity of recurrence and efficacy of SoC were obtained from MODIFY I/II trials [24] for each subgroup (Table 1). Second and third recurrence rates, colectomy rates, mortality, costs and utilities were obtained from the literature (Table 2). Adverse events were not considered as the overall rates showed in MODIFY I/II trials were similar with bezlotoxumab and placebo [24].

Conservative assumptions were made if no data were available.

Recurrence

The rates of first recurrence for bezlotoxumab + SoC and SoC alone were taken from MODIFY I/II trials for each subgroup (Table 1). The duration of bezlotoxumab efficacy was assumed to be 12 weeks, corresponding to the follow-up period in the MODIFY I/II trials. Subsequent recurrence rates were based on a review of the literature on patients at high risk of recurrent CDI [25] and expert opinion (Table 2).

Efficacy of SoC

The clinical cure rates from the MODIFY I/II trials were used to estimate the efficacy of SoC for each subgroup (Table 1). The following assumptions were made: SoC efficacy at managing the index case was based on the data from subjects without a previous episode; SoC efficacy at managing the first recurrence was based on the data from subjects with one previous episode; and SoC efficacy at managing the subsequent recurrence was based on the data from subjects with two or more episodes.

Table 1 Model parameters for each subgroup based on MODIFY I/II trials [24]

Parameters	Age ≥ 65 years	Severe CDI	Immunocompromised	≥ 1 Episodes of CDI in previous 6 months	Age ≥ 65 years and ≥ 1 episodes of CDI in previous 6 months
Age, years (median)	76.58	70.99	60.7	66.11	77.00
Female, %	57.86	53.44	49.24	54.94	55.50
Patients entering the model with severe CDI, %	25.40	100.00	18.79	12.29	17.60
30 days recurrence rate (first) on bezlotoxumab + SoC, %	15.38	10.66	14.61	25.00	19.38
30 days recurrence rate (first) on SoC, %	31.36	22.40	27.45	41.10	43.38
Proportion of recurrences that are severe, %	15.63	41.67	15.52	4.72	8.33
SoC efficacy for index case, %	81.26	71.67	83.72	80.67	77.70
SoC efficacy for first recurrence, %	76.74	62.16	71.67	80.67[a]	77.70[a]
SoC efficacy for subsequent recurrence, %	80.77	66.67	76.47	82.14	80.34

CDI C. difficile infection; *SoC* standard of care
[a] Model assumption: efficacy for first recurrence = efficacy for index case

Colectomy

The risk of colectomy and the mortality risk in patients requiring colectomy were based on a prospective cohort Spanish study [26], whose aim was to evaluate the frequency, associated risk factors and prognosis of first CDAD recurrences, and a literature review [27].

Mortality

The model assumes that the CDI-associated mortality risk is higher during the first 180 days after infection for patients who suffer a recurrence (36.3%) compared to those experiencing a sustained response (25.7%) based on Olsen et al. [28], who estimated the 6-month mortality in patients with recurrent CDI compared with patients with CDI who did not develop a recurrence in a retrospective cohort of hospitalized patients. Given the lack of evidence, it was assumed, based on Olsen et al. [28], that there is no CDI-associated mortality after 180 days; therefore, the mortality rate returns to that specified by the Spanish life tables [29] after that time.

Utility Values

Utility values for the different health states were derived from the published literature (Table 2). Wilcox et al. [30] conducted a retrospective study on resource use and health-related quality of life (HRQoL) associated with recurrent CDI

Table 2 Model parameters for all subgroups based on literature review

Parameter	All subgroups	References
Bezlotoxumab (Zinplava®) acquisition cost, €	€2950	[20]
Fidaxomicin (Dificlir®) acquisition cost, €	€1500	[20]
Recurrence rate (second), %	45.0	[25]
Recurrence rate (third), %	45.0	Expert opinion
Colectomy, %	1.8	[36]
Death after colectomy, %	40.0	[36]
All-cause mortality (180-days after CDI), %	25.7 (patients without subsequent recurrences)	[28]
	36.3 (patients with ≥ 1 subsequent recurrences)	
Utility value—CDI mild/moderate	0.42	[30]
Utility value—CDI severe	0.42	[30]
Utility value—colectomy	0.42	[30]
Utility value—clinical failure	0.42	[30]
Utility value—post-colectomy	0.79	[31]
Utility value—clinical cure, post-clinical failure	Baseline utility value	[32]
	Males: decreasing from 0.971 (18–24 years old) to 0.846 (75 years old or above)	
	Females: decreasing from 0.965 (18–24 years old) to 0.725 (75 years old or above)	
Cost of first recurrence, € (2017)	€5006.6	[17]
Cost of second and third recurrence, € (2017)	€6075.7	[17]

CDI C. *difficile* infection

hospitalizations in the UK. For the purpose of the model, the same utility value was assumed for health states "CDI mild/moderate", "CDI severe", "colectomy" and "clinical failure" based on Wilcox et al. [30]. The utility value for "post-colectomy" was obtained from a publication by Brown et al. [31], who investigated long-term HRQoL among patients who had undergone a colectomy within the previous 10 years. The baseline utility values from the general population were assumed to be applicable for "clinical cure" and "post-clinical failure" health states [32].

Costs

The cost inputs considered in the cost-effectiveness analysis were bezlotoxumab drug acquisition [20] and CDI episode (first, second and third recurrence) costs.

Consistent to MODIFY I/II trials [19], participants in both arms were receiving the same SoC (metronidazole, vancomycin and/or fidaxomicin) for 10–14 days; therefore the cost of SoC was not included as it would have no effect on the cost-effectiveness results.

The cost per episode of CDI was estimated based on Asensio et al. [17], who estimated the

costs of CDI in Spain from the NHS perspective including antimicrobials (metronidazole, vancomycin), hospitalization, surgical procedures, measures to control the infection and recurrences of treated infections. It should be noted that the costs were estimated before the introduction of fidaxomicin, which is expensive compared to other SoC and often used for later recurrences. Therefore, the costs of managing recurrence may be underestimated leading to an underestimation of the cost savings associated with bezlotoxumab. This assumption was specifically addressed in a sensitivity analysis.

Costs were inflated to 2017 euros (€), where appropriate, using the Spanish consumer price index [33].

ANALYSIS

Model Outputs

Model outcomes included the number of recurrences (first, second, third and total), the number needed to treat (NNT) to prevent one recurrence, 180-day mortality, life-years, quality-adjusted life years (QALYs) and costs for each treatment.

The cost-effectiveness analysis outcomes were expressed as the cost per recurrence avoided and cost per QALY gained. The incremental cost-effectiveness ratio (ICER) was estimated for bezlotoxumab added to SoC compared to SoC alone.

Sensitivity Analysis

Deterministic (DSA) and probabilistic sensitivity analysis (PSA) were performed in order to assess the impact of uncertainty on the ICER.

In DSA, the upper and lower bounds of the 95% confidence intervals were tested for each parameter (see Tables S1–S5 in the electronic supplementary material for details). When the confidence interval was not available or could not be estimated based on the literature, it was estimated assuming that the standard error was 5% of the base case value. Additionally, scenario analyses were performed in order to explore the

variation of all utility's values at the same time (extreme values) and the addition of the drug acquisition cost of fidaxomicin (Table 2) to CDI episode costs. Results of DSA were expressed as tornado charts.

PSA was performed with 1000 Monte Carlo simulations. The probabilities and utility values followed a beta distribution, costs followed a gamma distribution and for utility multipliers that have a base case value of 1, a triangular distribution with a mode of 1 was assumed (see Tables S6–S10 in the electronic supplementary material for details). Parameterization was based on the published literature where available. When no information on uncertainty could be sourced, the standard error was assumed to be 5% of the base case value. ICER scatter plots and cost-effectiveness acceptability curves were constructed for each subgroup.

The probability of bezlotoxumab being cost-effective at the €21,000 per QALY gained willingness-to-pay (WTP) threshold recently established in Spain was estimated. Additionally, alternative thresholds at €30,000/QALY and €11,000/QALY were estimated as recommended specifically for sensitivity analysis [34].

Compliance with Ethics Guidelines

This article does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Base Case Scenario

Table 3 shows a summary of the results of the analysis. The addition of bezlotoxumab to SoC for the prevention of recurrence in patients at high risk of CDI recurrence compared to SoC alone was associated with a reduction in total recurrences and 180-day mortality and an increase in QALYs. The ICER was therefore €12,723.68, €17,494.70, €9544.72, €7386.38 and €4378.20 per QALY gained, for patients aged 65 years or older, clinically severe CDI, immunocompromised, with ≥ 1 CDI episode in

Table 3 Cost-effectiveness results for the prevention of CDI with bezlotoxumab + SoC vs. SoC in five patient population with CDI at increased recurrence risk

Results (bezlotoxumab + SoC vs. SoC)	Age ≥ 65 years	Severe CDI	Immunocompromised	≥ 1 Episodes of CDI in previous 6 months	Age ≥ 65 years and ≥ 1 episodes of CDI in previous 6 months
Incremental total recurrences, %	− 26.4	− 19.5	− 21.2	− 26.6	− 39.7
Incremental 180-day mortality, %	− 1.7	− 1.1	− 1.3	− 1.7	− 2.5
NNT	3.8	5.1	4.7	3.8	2.5
Incremental cost, €	1515.5	1889.67	1797.33	1504.85	794.57
LY gained	0.15	0.13	0.22	0.24	0.22
Incremental QALYs	0.12	0.11	0.19	0.20	0.18
Cost per recurrence avoided, €	5735.97	9681.42	8465.27	5653.53	2001.46
ICER, €/QALY gained	12,723.68	17,494.70	9544.72	7386.38	4378.20

CDI C. difficile infection, *ICER* incremental cost-effectiveness ratio, *LY* life year, *QALY* quality-adjusted life year, *SoC* standard of care

the previous 6 months, and aged ≥ 65 years or older and ≥ 1 CDI episode in the pre vious 6 months, respectively.

Sensitivity Analysis

Deterministic Sensitivity Analysis
In the DSA, the model parameters that resulted in the highest degree of variability in the ICER were recurrence rate (first), all-cause mortality (180-days after CDI), and utility value for clinical cure health state (Fig. 2). In the subgroups of patients with ≥ 1 CDI episode in the previous 6 months and in patients aged ≥ 65 years and with ≥ 1 CDI episode in the previous 6 months, all analyses were below the €21,000 per QALY gained threshold.

Probabilistic Sensitivity Analysis
PSA results showed that bezlotoxumab was cost-effective at the €21,000 per QALY gained threshold for most of the simulations performed (Table 4). ICER scatter plots and cost-effectiveness acceptability curves for each

subpopulation are presented in Figs. 3 and 4, respectively.

DISCUSSION

Bezlotoxumab is the first and only drug indicated to prevent recurrences of CDI in high-risk patients. Therefore, its approach is different from antibiotics, which are licensed only to treat the infection. The model developed in the present study has shown that the addition of bezlotoxumab to SoC for the prevention of recurrence in five populations of patients at high risk of CDI recurrence was associated with an ICER below the €21,000 per QALY gained threshold [34] relative to SoC alone over a lifetime horizon from the perspective of the Spanish NHS. As expected, the lowest ICER (€4378.20 per QALY gained) was estimated for the subpopulation of patients aged 65 years or older with a history of CDI episodes, who achieved more health benefits, in terms of prevented recurrences and 180-day mortality, with a lower incremental cost of bezlotoxumab
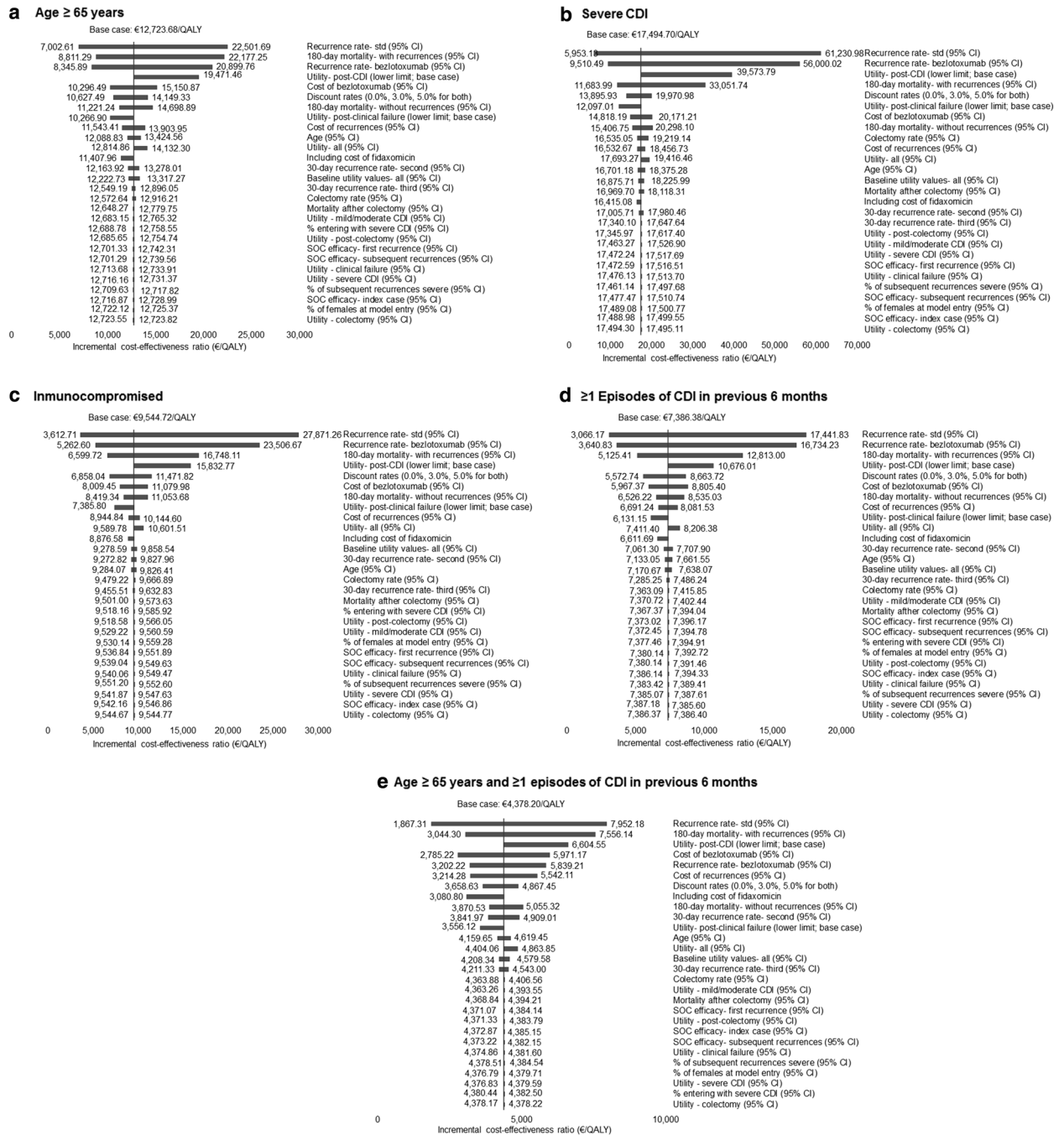
Fig. 2 Tornado charts of bezlotoxumab added to SoC compared to SoC alone

added to SoC compared to SoC alone. We also found that the probability of bezlotoxumab being cost-effective with a WTP of €21,000 per QALY gained [34] was high in all subgroups.

As mentioned before, a previous study evaluated the cost-effectiveness of bezlotoxumab

added to SoC compared to SoC alone in six subgroups of patients at risk of CDI recurrence by using the same economic model [22]. Consistent with the US analysis, the present study showed similar ICER for the subgroups that were common between studies: ≥ 65 years of

Table 4 Probability of bezlotoxumab + SoC being cost-effective vs. SoC (%) at different willingness-to-pay thresholds

Threshold	≥ 65 years old	Severe CDI	Immunocompromised	≥ 1 CDI episodes in previous 6 months	≥ 65 years old and with ≥ 1 CDI episodes in previous 6 months
€11,000/ QALY gained	34.47	23.08	55.74	72.13	97.10
€21,000/ QALY gained	85.51	54.14	86.01	94.51	99.60
€30,000/ QALY gained	95.80	74.53	93.71	98.10	100.00

CDI C. difficile infection, *QALY* quality adjusted life years

age ($15,298 vs. €12,723.68 per QALY gained), immunocompromised ($12,597 vs. €9544.72 per QALY gained), patients with a clinically severe CDI episode ($21,430 vs. €17,494.70 per QALY gained), and patients ≥ 65 years of age with ≥ 1 episodes of CDI within the previous 6 months ($3591 vs. €4378.20 per QALY gained). It should be noted that, according to DSA, the main parameters influencing cost-effectiveness results were recurrence rate (first) [19], 180-days mortality [28], and utility value for clinical cure health state [32], and our analysis used similar data to the US model for these parameters.

As with any model, there are some limitations in the present analysis, mainly related to input availability and model assumptions. First, in the absence of published studies measuring utility among patients with CDI, natural progression of disease or updated costs from the Spanish setting, some sources of the input parameters used were based on different populations and some assumptions reported in methods needed addressing. It should be noted that, although a higher recurrence rate after the second recurrence has been reported [25], the clinical experts assumed 45% should be applied to all subsequent recurrences as a conservative assumption. Further studies are required to obtain all these data. Second, regarding model structure, it was assumed that patients in post-clinical failure health state would not experience any recurrence of CDI since these patients were not tracked in MODIFY I/II trials. Although this might be seen as a conservative approach, as patients experiencing clinical failure would be treated and eventually cured, considering recurrences after clinical failure would lead to even higher benefits for those patients. Third, as most clinical input parameters of the model were based on MODIFY I/II trials, in which the evaluation of CDI severity was based on the Zar score, the proportion of patients with a severe CDI is probably underestimated, since more than 90% of participants were receiving SoC when scoring was performed [19]. Fourth, the cost of recurrence was based on a Spanish study which did not include fidaxomicin as it was conducted prior to its introduction. Fidaxomicin is expensive compared to vancomycin and metronidazole, and therefore the cost savings associated with bezlotoxumab may be underestimated. This point was addressed and confirmed in the DSA, which showed a lower cost associated with bezlotoxumab in the scenario analysis (addition of the drug acquisition cost of fidaxomicin to CDI episode costs) compared with the base case. ICER was 10.34, 6.17, 7.00, 10.49 and 29.63% lower for patients aged 65 years or older, clinically severe CDI, immunocompromised, with ≥ 1 CDI episode in the previous 6 months, and aged ≥ 65 years or older and ≥ 1 CDI episode in the previous 6 months, respectively, compared with the base
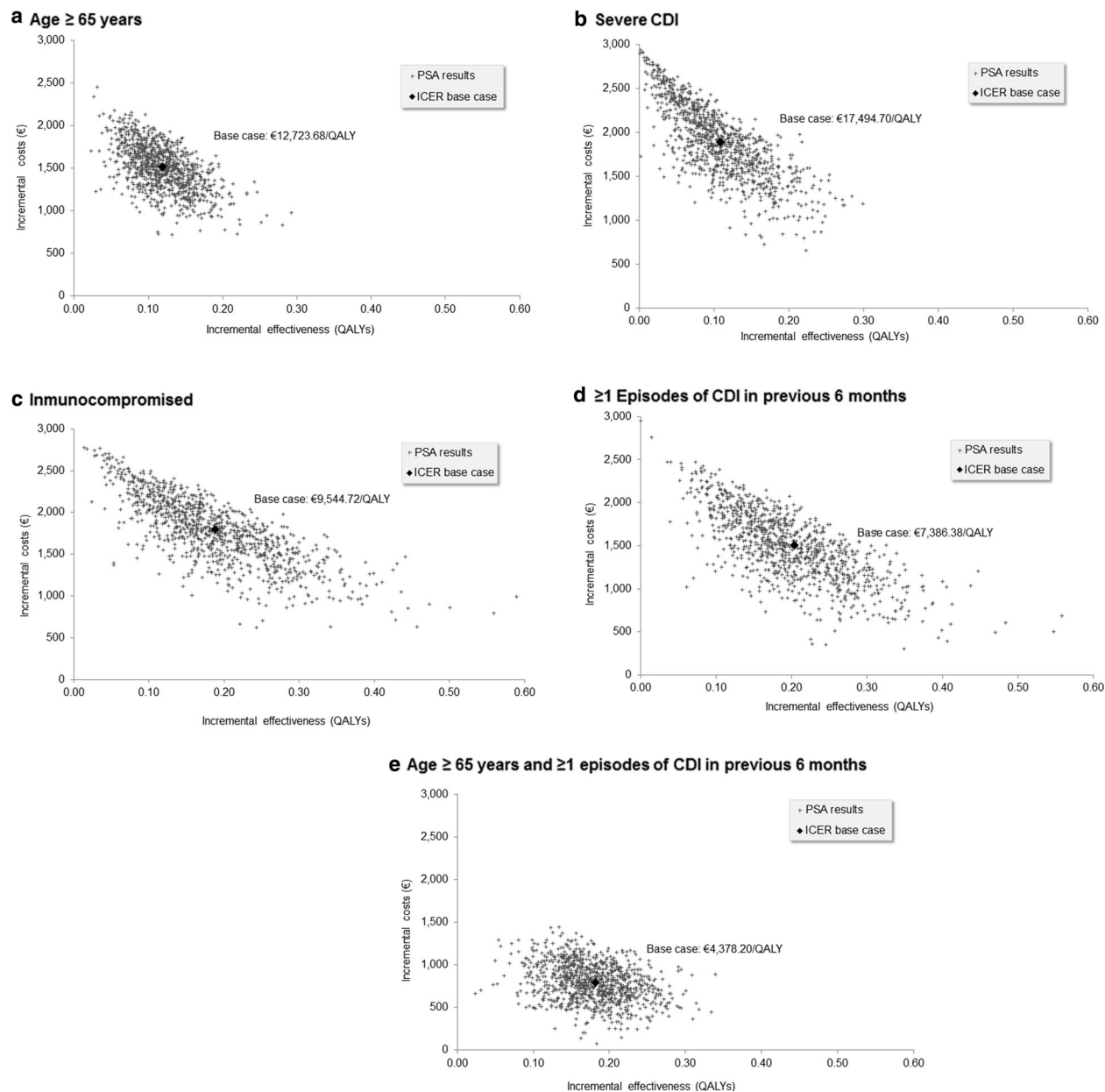
Fig. 3 Cost-effectiveness scatter plots of bezlotoxumab added to SoC compared to SoC alone

case. On the other hand, it should also be noted that, in the MODIFY I/II trials, the population treated with fidaxomicin was small compared with that treated with vancomycin and metronidazole. Thus, if the population treated with fidaxomicin were larger, it could be expected that its greater efficacy (clinical cure) would have an effect on the results of cost-effectiveness. However, as stated in the model,

the efficacy (clinical cure) of SoC is the same for both treatment and comparison arms and therefore an increase in the efficacy of SoC should not to have a significant effect on ICER. This fact has been equally addressed and confirmed by the DSA, showing minimal changes in ICER by varying the effectiveness of SoC in each subgroup. Fifth, the current analysis is unable to capture the transmission of the
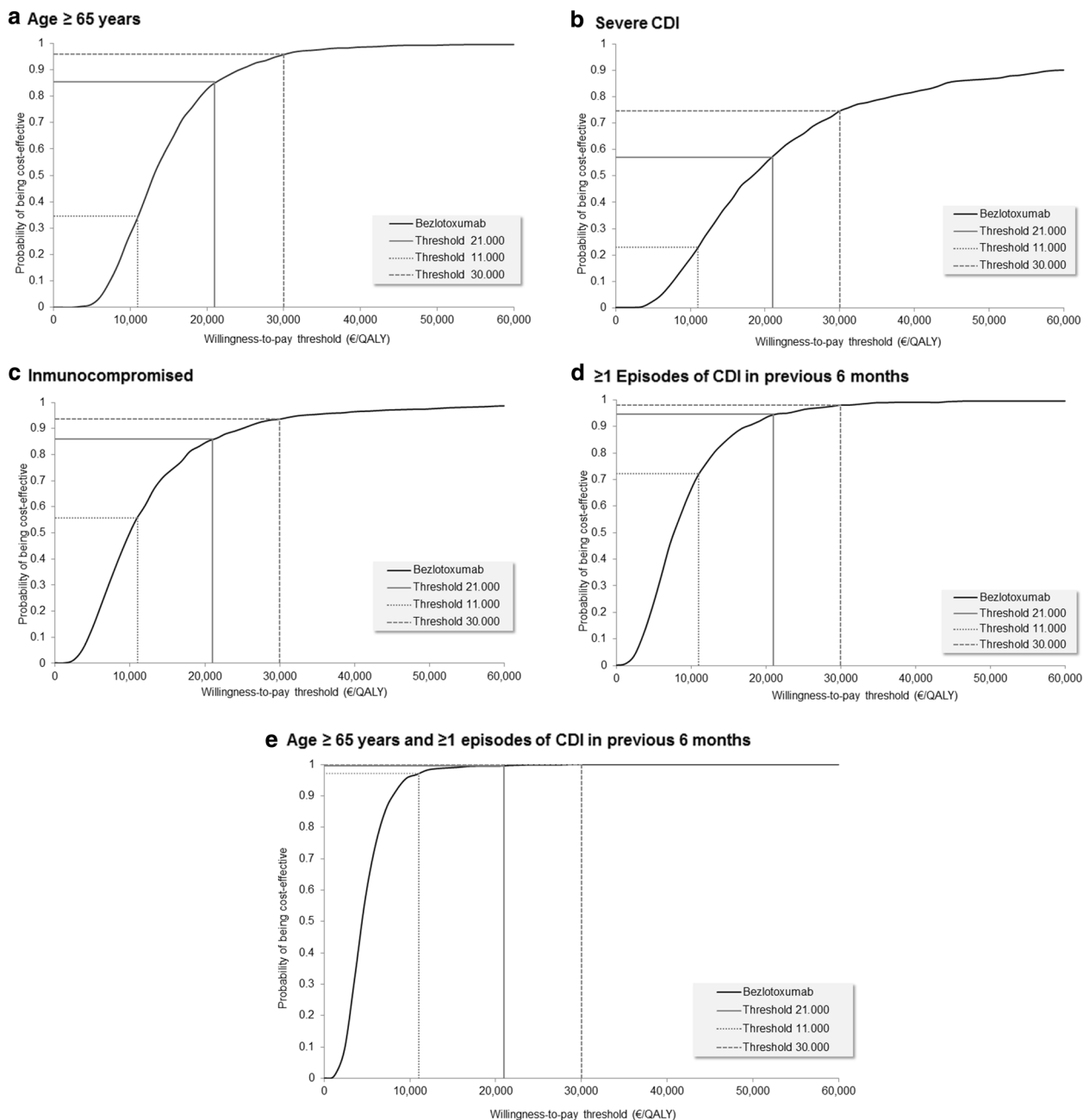
Fig. 4 Cost-effectiveness acceptability curves of bezlotoxumab added to SoC compared to SoC alone

disease CDI. Patients who experience recurrent CDI have a high probability of repeating courses of antibiotic treatment, of adverse events as well as re-hospitalization, and acting as a reservoir of infection that can lead to secondary infection in other vulnerable patients [1]. Consequently, the ability of bezlotoxumab to prevent CDI recurrences should also have an impact on the

overall incidence of CDI. Lastly, the cost-effectiveness analysis was carried out from the perspective of the Spanish NHS, which may underestimate the societal impact of the use of bezlotoxumab, such as time lost due to CDI or the cost of formal or informal caregivers.

Despite these limitations, a conservative approach has been adopted for this model,

suggesting that the effectiveness of bezlotoxumab could be underestimated. Future investigations should address capturing the transmission of the disease, estimating the impact of the prevention of recurrence on the overall incidence of CDI and taking indirect costs and out-of-pocket costs incurred by the patient into account.

Although the findings reported in this study may be relevant to the Spanish healthcare system alone, approaches that can reduce CDI-associated resource use and costs should be of general interest [35], and the model can be adapted to other European countries.

CONCLUSIONS

In conclusion, the results suggest that bezlotoxumab added to SoC compared to SoC alone is a cost-effective treatment to prevent the recurrence of CDI in high-risk patients from the perspective of the Spanish NHS being the ICER below 21,000 per QALY gained in all subgroups. Deterministic sensitivity analysis showed results to be sensitive to variation in some parameters, specifically the recurrence rate (first) and all-causes mortality had a higher impact on the ICER in patients aged $\geq$ 65 years old, patients with severe CDI and patients with compromised immunity by establishing it above the threshold. Probabilistic sensitivity analysis determined that the probability that bezlotoxumab was cost-effective at a willingness-to-pay threshold of €21,000/QALY was 85.5, 54.1, 86.0, 94.5 and 99.6%, for patients aged 65 years or older, clinically severe CDI, immunocompromised, with $\geq$ 1 CDI episode in the previous 6 months, and aged $\geq$ 65 years or older and $\geq$ 1 CDI episode in the previous 6 months, respectively.

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